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Morphine In Myocardial Infarction: Delay In Platelet Inhibition Due To Morphine Administered To Patients Presenting With Acute Coronary Syndrome

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Abstract
Background:

The American College of Cardiology Foundation/American Heart Association Task Force recommends morphine for patients with ST-elevation myocardial infarction and for patients undergoing primary percutaneous coronary intervention (PPCI). A drug-to-drug interaction between morphine and the preferred antiplatelets have been studied to determine the adverse effects on such a combination in antiplatelets. There is an increase risk of thrombic events if platelets are not effectively inhibited during PPCI. The primary aim of this systematic review is to clarify which effects exist on the efficacy of antiplatelet from co-administration of morphine in the setting of acute coronary syndrome (ACS). The secondary aim is to determine if the dose or type of the antiplatelet is a means to overcome the effects of morphine or whether the use of morphine use in ACS should be questioned as it could possibly lead to treatment failure.

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An exhaustive search of the available medical literature was conducted using MEDLINE-Ovid, CINAHL, and Web of Science. Keywords included: morphine, myocardial infarction, STEMI, acute coronary syndrome, antiplatelet, prasugrel, ticagrelor, clopidogrel. Relevant articles were assessed using the Grading of Recommendations, Assessment, and Evaluation (GRADE) system.

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The initial search of databases resulted in 649 studies. Application of eligibility criteria and elimination of duplicates narrowed the search down to 7 studies. With further exclusion criteria applied, 4 studies remained. Three of the remaining studies were randomized, double-blind, placebo-controlled, cross-over trials. One final study was a patient-level integrated analysis. The antiplatelets focused on in the studies were: clopidogrel, ticagrelor, and prasugrel. All 4 studies showed an impact of morphine on the pharmacodynamics of each platelet and the pharmacokinetics of some of the antiplatelets.

Conclusion:

Morphine co-administered with antiplatelets in patients with STEMI has the potential to diminish the effects of specific $P2Y_{12}$ inhibitors. Morphine diminishes pharmacodynamic effects in all recommended antiplatelets and diminishes pharmacokinetics in certain antiplatelets as well. As emerging evidence continues to show the negative impacts of morphine in patients with ACS, clinicians need to be judicious in their use of morphine when co-administered with an antiplatelet.

Keywords: Morphine, antiplatelet, clopidogrel, ticagrelor, prasugrel, acute coronary syndrome, PPCI, myocardial infarction, STEMI

Degree Type
Capstone Project

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Biography

[Redacted for privacy]

Abstract

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The American College of Cardiology Foundation/American Heart Association Task Force recommends morphine for patients with ST-elevation myocardial infarction and for patients undergoing primary percutaneous coronary intervention (PPCI). A drug-to-drug interaction between morphine and the preferred antiplatelets have been studied to determine the adverse effects on such a combination in antiplatelets. There is an increase risk of thrombic events if platelets are not effectively inhibited during PPCI. The primary aim of this systematic review is to clarify which effects exist on the efficacy of antiplatelet from co-administration of morphine in the setting of acute coronary syndrome (ACS). The secondary aim is to determine if the dose or type of the antiplatelet is a means to overcome the effects of morphine or whether the use of morphine use in ACS should be questioned as it could possibly lead to treatment failure.

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Morphine co-administered with antiplatelets in patients with STEMI has the potential to diminish the effects of specific $P2Y_{12}$ inhibitors. Morphine diminishes pharmacodynamic effects in all recommended antiplatelets and diminishes pharmacokinetics in certain antiplatelets as well. As emerging evidence continues to show the negative impacts of morphine in patients with ACS, clinicians need to be judicious in their use of morphine when co-administered with an antiplatelet.

Keywords: Morphine, antiplatelet, clopidogrel, ticagrelor, prasugrel, acute coronary syndrome, PPCI, myocardial infarction, STEMI

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List of Abbreviations

ACS	Acute Coronary Syndrome
AUC	Area under the curve
GRADE	Grading of Recommendation, Assessment, Development, and Evaluation
HRPR	High Residual Platelet Reactivity
LD	Loading Dose
MI	Myocardial Infarction
NSAIDS	non-steroidal anti-inflammatory drugs
NSTEMI	Non-ST-segment elevation Myocardial Infarction
PO	Orally, by mouth
PPCI	Primary Percutaneous Coronary Intervention
PRU	Platelet residual activity
RCT	Randomized control trial
STEMI	ST-segment elevation Myocardial Infarction
VASP	Vasodilator-stimulated-phospho-protein phosphorylation

Morphine in Myocardial Infarction: Delay in Platelet Inhibition due to Morphine Administered to Patients Presenting with Acute Coronary Syndrome

BACKGROUND

In 2009, approximately 683 000 patients were discharged from US hospitals with the diagnosis of ACS. About 25-40% of acute myocardial infarction presentations are ST-elevation myocardial infarctions (STEMI).[1-3] Reperfusion therapy is recommended for patients with STEMI, specifically in those presenting to the ER within 12 to 24 hours who also have symptoms of ongoing ischemia and with associated EKG changes. For these patients, Primary percutanous coronary intervention (PPCI) is the preferred strategy.[1,2, 4-6] Initial treatment for chest pain associated with an MI is intravenous morphine (4-8 mg initially followed by 2-8 mg every 5-15 minutes).[1-2] Morphine can lessen anxiety, support breathing, and help ventricular loading conditions.[1-2] In patients who meet eligibility criteria and undergo PPCI for STEMI, it is recommended to provide patients with a loading dose (LD) of a $P2Y_{12}$ receptor inhibitor early and prior to PPCI, in addition to a dose of aspirin between 162 to 325 mg. The choices of $P2Y_{12}$ inhibitors are: clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 184 mg.[2]

It is gathered only from expert opinion to administer morphine for pain control in patients with an MI. The benefit of morphine in this population has not been proven through sufficient randomized control trials (RCT).[7,8] In patients with STEMI, morphine has even been associated with higher mortality and less effective reperfusion after PPCI.[9-11] The ATLANTIC trial[13] found that patients who did not receive morphine when diagnosed with STEMI, had considerable improvement in the

EKG readings, stating these patients also had a significant P value for interaction between morphine use and time of ticagrelor administration.[7,12,14]

In 2012, Parodi et al[7] conducted a randomized study to investigate the onset times of the newer $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) in STEMI. In this study, it was hypothesized that there was an associated delayed antiplatelet effect caused by morphine use in the first hours of a STEMI.[7,15] Morphine became an independent predictor of high residual platelet reactivity (HRPR) (OR: 5.29; 95% CI: 1.44 to 19.49; p=0.012).[15] Shortly following, Hobl et al[8] looked at the interaction of Morphine with Clopidogrel, finding that morphine does indeed decrease plasma concentrations and effects of Clopidogrel. After these studies, there have been very few trials performed to assess the true drug-to-drug interaction of morphine and antiplatelets in trying to determine which antiplatelet, if any, has the least decrease in efficacy when co-administered with morphine.

The primary aim of this systematic review is to clarify which effects exist on antiplatelet efficacy from co-administration of morphine in the setting of ACS. The secondary aim is to determine if the dose of the antiplatelet is a means to overcome the effects of morphine or whether the overall use of morphine in ACS should be questioned. Understanding of antiplatelet effects of morphine may challenge the overall benefit of morphine use in patients with ACS and cause providers to think about possible other forms of pain control which do not pose a risk of treatment failure due to delay in platelet inhibition.[8]

METHODS

An exhaustive search of the available medical literature was performed using MEDLINE-Ovid, CINAHL, and Web of Science. The keywords included: morphine, myocardial infarction, STEMI, acute coronary syndrome, antiplatelet, prasugrel, ticagrelor, clopidogrel. The search was narrowed to include articles between the years 2010 and 2016. Exclusion criteria applied to studies not in the English or Spanish language and trials on animals. Articles were excluded if they did not look specifically at the effects of morphine on antiplatelets in myocardial infarction. Bibliographies of each article were further searched for relevant sources. Chosen articles were assessed for quality using the Grading of Recommendations, Assessment, and Evaluation (GRADE).[16]

RESULTS

The initial search of databases resulted in 649 studies. Application of eligibility criteria and elimination of duplicates narrowed the search down to 7 studies. With further exclusion criteria applied, 4 studies remained. Three of the remaining studies were randomized, double-blind, placebo-controlled, cross-over trials.[8,9,17] One final study was a patient-level integrated analysis.[7] See Table I and Figure I. The selected antiplatelets for study included: clopidogrel, ticagrelor, and prasugrel. The three RCTs[8,9,17] each studied a different antiplatelet whereas the observational study[7] used both prasugrel and ticagrelor as the chosen antiplatelets to study. Dosing of the antiplatelets was determined by Task Force Guidelines.[1] Each was a loading dose. The dose of clopidogrel studied was 600mg.[8] The dose of prasugrel was 60 mg PO.[7,17] The dose of ticagrelor was either 180

mg[7,9] or 360 mg.[7] The use of 360 mg was in the observational study[7] and this was a decision made by the provider in the emergent situation.

The three randomized controlled trials[8,9,17] included patient volunteers who were all deemed to be healthy. In the observational trial[7], the patients underwent PPCI after diagnosis of STEMI. In each study, the patients received the recommended dose of 5 mg of intravenous morphine co-administered with the chosen antiplatelet.[7-9,17,1] In the studies that used a control, the chosen placebo was 0.9% NaCl.[8,9,17]

The trials examined high residual platelet reactivity (HRPR) at various times after morphine was co-administered with a loading dose of the selected antiplatelet. In each study, high residual platelet reactivity was defined as $P2Y_{12}$ reactivity units (PRU) $\geq$ 208.[7-9,17] Each trial used the HRPR measurements to determine the pharmacodymanic and pharmacokinetic effects of morphine on the antiplatelet. See Table II for summary of findings.

Parodi et al Study on Morphine Interaction with Ticagrelor or Prasugrel

This patient-level integrated analysis[7] sought to examine the effects of morphine on platelet inhibition in patients diagnosed with a STEMI undergoing PPCI. The researchers investigated three hundred patients, all $P2Y_{12}$ inhibitor naïve across 5 different studies.[15,18-20] Each patient received a loading dose of either prasugrel (n=95) or ticagrelor (n=205) and underwent PPCI. They assessed platelet reactivity in the plasma to determine the interaction of morphine and the antiplatelet. Patients were either treated with morphine or not treated with morphine based on the discretion of the health care provider overseeing the patient.[7]

In addition to the specific antiplatelets in question, the following antithrombotic agents were also given at the time of PPCI: Aspirin 300 to 500 mg LD followed by 100 mg, bivaliriduin 0.75mg/kg bolus followed by 1.75 mg/kg/h infusion or unfractionated heparin 70 UI/kg bolus followed by additional boluses in order to achieve an activated clotting time of 250-300 seconds during PPCI.[7]

Parodi et al stated there eligibility criteria including: a diagnosis of STEMI within 12 hours of symptom onset. Exclusion criteria included: age less than 18 years, active bleeding or bleeding diathesis, previous ischemic attack or stroke, administration of ticlopidine, clopidogrel, prasugrel, ticagrelor, or glycoprotein IIb/IIIa inhibitors in the week prior to the event, need for chronic anticoagulant therapy, known relevant hematologic deviations, life expectancy less than one year, known severe renal or liver disease, and hemodynamic instability.[7] The primary endpoint was residual platelet reactivity measured by VerifyNow specifically 2 hours after LD. Secondary endpoints were the percentage of patients with HRPR at 2 hours from administration of the LD and the incidence of vomit (which will not be discussed in this systematic review).[7]

Parodi et al state the differences between patients at baseline included: lower body mass index, bivalirudin use, and higher systolic blood pressure in those treated with morphine. The study looked at the antiplatelet agents, ticagrelor and prasugrel. High residual platelet reactivity (HRPR) was assessed using VerifyNow at 1, 2, and 4 hours post loading dose. At the end of the study, the researchers found no significant differences between prasugrel and ticagrelor. The researchers state it was found that at 2 hours after the loading dose, the $P2Y_{12}$ reactivity units were 187 (153-221) and 133 (102-

165) in patients with and without morphine, respectively. HRPR at 2 hours was found in 53 and 29% of patients with and without Morphine (P<0.0001), respectively.[7]

The researchers state the result was that patients receiving morphine had a higher PRU as compared to those who did not: 182.3 PRU (95% CI, 164.2-200.3) with morphine and 140.3 PRU (95% CI, 128.2-152.4) without morphine (with a mean difference of 42.0 PRU (95% CI, 19.8-64.1), P<0.001). They explain the PRU values at 2 hours, which was the primary endpoint, were 187.3 (153.4-221.2) and 133 (102.3-165.0) with and without morphine (P<0.001), respectively. Parodi et al report that even up to 4 hours post LD, the same differences remained. The researchers found there to be two independent predictors of HRPR, which included: Morphine use (odds ratio, 2.91 [1.71-4.97]; P<0.0001) and age (odds ratio, 1.03 [1.01-1.05]; P=0.010). The study reports that morphine remained associated with HRPR even after propensity score adjustment (c-statistic, 0.68; 95% CI, 0.66-0.70; P=0.879 for Hosmer-Lemeshow test). Overall, the researchers state that morphine was associated with an increased risk of HRPR several hours after LD using either the 208 or 230 threshold: risk ratio = 1.55 (95% CI, 1.28-1.87), P<0.001 and risk ratio = 1.44 (95% CI: 1.20-1.86), P<0.001. Worth noting is a possible dose response gradient in PRU or HRPR in patients taking either the 180 mg or 360 mg dose of ticagrelor.[7]

The authors concluded that in patients with STEMI, morphine use is associated with a delay in onset of action of oral antiplatelet agents due to inefficient slowing of platelet reactivity. They state this effect remained consistent in patients treated with either prasugrel or ticagrelor. The inhibitory effect of morphine was evident up to 4 hours after loading doses of antiplatelets.[7] This study was performed after previous studies of the less

potent antiplatelet, clopidogrel, was found to also have an suboptimal antiplatelet effect by Morphine.[7,21-23]

The authors conclude their research with supporting statements from previous studies and discussion points on the use of morphine. They mention a previous study[24] on delayed absorption and gastric emptying due to morphine, which poses a biological rather than drug to drug interaction causing the decreased plasma levels of orally administered drugs.[7,24] Morphine may also be given to patients who are at higher risk and more actuely ill. These patients may have differences in hemodynamics, adrenergic activation, and systemic vasoconstriction causing reduction of blood volume to the abdomen. These differences may result in a delay in drug adsorption and reduced platelet inhibition.[7] The authors conclude that caution should be demonstrated with morphine use in STEMI patients because there is great importance of platelet inhibition for these patients when treated by PPCI and there is such a lack of adequate data supporting the use of morphine.[7] See Table II for summary of findings.

A limitation of this study is that was an observational study rather than an RCT. HRPR is not a precise equivalent to measure platelet effect. Another limitation is that this study only studied pharmacodynamics and not pharmacokinetics of the antiplatelets.[7]

Hobl et al Study on Morphine Interaction with Clopidogrel

This randomized, double-blind, placebo-controlled, cross-over trial[8] sought to study the potential drug-to-drug interactions between clopidogrel and morphine. The researchers chose to look at clopidogrel due to its relatively slow onset of action as it is a pro-drug that requires metabolic activation in 2 steps by cytochrome P450 enzymes.[8,25]

The study took 24 healthy volunteers and co-administered 600 mg clopidogrel with either placebo or the recommended 5-mg morphine dose.[8,1] The researchers looked at the pharmacokinetics of clopidogrel as well as its antiplatelet effects. The inclusion criteria of the sample size was: greater than or equal to 18 years of age, non-pregnant, and the ability to comprehend the full nature and purpose of the study. The exclusion criteria were: intake of NSAIDS or other platelet inhibitors, known coagulation disorders, renal or liver disease, chronic infectious diseases, clinically relevant abnormal laboratory values, and contraindications to clopidogrel or morphine.[8]

The trial was randomized, and although the pharmacists preparing the controls and treatments were unblinded, the physcians administering them were blinded. Those who analyzed the pharmacokinetics and pharmacodynamics were also blinded. After an overnight fast by the patients, physicians gave them a LD of 600 mg clopidogrel. The VASP assay and multiple electrode aggregometry were used to measure the clopidogrel effects. The researchers assessed pharmacokinetics using liquid chromatography tandem mass spectrometry. Pharmacokinetic calculations were made using Kinetica 2000 version 3.0.Hobl et al describe that the subjects were also genotyped for CYP2C9 and CYP2C19 polymorphisms to allow for comparisons of the effect size of morphine with genetic determinants of clopidogrel pharmacokinetics. Before the crossover trial began, the trial allowed for a fourteen-day washout period.[8]

The results showed a direct delay in clopidogrel absorption when administered with morphine ($p=0.025$) and a reduced area under the curve (AUC) levels of its active metabolite by 34% ($p=0.001$). They state that morphine delayed the maximal inhibition of platelet aggregation on average by 2 hours ($n=24$; $p<0.001$) and residual platelet

aggregation was higher 1 to 4 hours after morphine injection (n=24; p<0.005). The researchers state that morphine also delayed the inhibition of the platelet plug formation under high shear rates (n=21; p<0.004). They concluded that this delay in clopidogrel absorption, decrease in plasma levels of the active metabolite, and the slowing and diminishing of its effect can lead to potential treatment failure in susceptible patients.[8]

The researchers found that in regards to the pharmacokinetic interactions of morphine and clopidogrel, morphine delayed maximal plasma concentrations of clopidgrel (T_{max}: 105 vs 83 min, P=0.025) and reduced the maximum serum concentration (C_{max}) of the clopidogrel active metobolite (from 171 to 113 ng/ml, P=0.025) and the total exposure was measured by the AUC_{0-n} by 34% (16 840 vs 11 103 ng/ml, p=0.001).[8] Hobl et al state that morphine delayed the time required to maximally inhibit platelet aggregation (3 vs 1.25 hours, P<0.001) which shows a significant effect in pharmacodymaics. Residual platelet aggregation was higher 1 to 4 hours after morphine injection (P<0.005)(n=24). Morphine also delayed the inhibition of platelet plug formation under high shear rates. The study states that clopidogrel intake prolonged the collagen/ADP induced closure time (CADP-CT-CT) 6 h after intake from a median of 110 to 162 seconds (P<0.01) under placebo but when morphine was co-administered, it did not have the same effect (105 to 106 seconds, P=0.97) (n=23; P=0.012 between treatments). Researchers stated clopidogrel reduced the median platelet reactivity index in the VASP phosphorylation assay from a median of 81% to 41% (n=10; P=0.008) and trend-wise less after morphine (87% vs 59%, P= 0.004; P=0.30 between treatments).[8] In regards to genetic polymorphisms in the patient population, researchers stated that

morphine caused a poor metabolizer phenotype in individuals genetically prone to extensively metabolized clopidogrel.[8]

The researchers closed their study with the discussion point that morphine slows clopidogrel absorption, decreases plasma levels of the active metabolite, and slows and diminishes clopidogrel effects. They stated that morphine effectively reduced the absorption of clopidogrel so that a 600 mg LD was equivalent to a 300 mg LD. Morphine delayed pharmacodynamics by about 2 hours. Hobl et al state that this potential lowering of the effective LD of clopidogrel may lead to adverse coronary outcomes including death.[26] The researchers assert that due to the results of their study, it is possible that co-administration of morphine and clopidogrel should be avoided, and one should consider using a more potent $P2Y_{12}$-inhibitor for greater efficacy when using morphine.[8] See Table II for summary of findings.

The trial discuss limitations of their study saying that VASP was only included on a subset of the participants as they did not begin using it as a measurement until partway through the study. They state the trial was not designed to measure differences between various types of metabolizers and the trial also did not measure the pharmacodynamics for 24 hours but it was evident that differences lessened after 4 hours. Another limitation, Hobl et al state, is that the study was performed on healthy patients instead of STEMI patients, whose absorption may be compromised through reduced splanchnic blood flow.[8,27]

Hobl et al Study on Morphine Interactions with Ticagrelor

This randomized, double-blind, placebo-controlled, cross-over trial[9] looked to study the potential drug-to-drug interactions between ticagrelor and morphine. The

researchers chose to look at ticegrelor because it is a more potent $P2Y_{12}$ inhibitor compared to clopidogrel, which was studied prior.[8] Ticagrelor does not need hepatic activation like clopidogrel does, so it has a quicker onset of effect, less variability in response between patients and higher efficacy.[9] Due to this mechanism of action, the researchers suspected that the drug interaction between morphine and clopidogrel could be overcome with the more potent ticagrelor.[9]

The study used 24 healthy volunteers with the inclusion criteria being: greater than or equal to 18 years of age, non-pregnant, and the ability to comprehend the full nature and purpose of the study. The exclusion criteria included: intake of NSAIDS or other platelet inhibitors, known coagulation disorders, renal or liver disease, chronic infectious diseases, clinically relevant abnormal laboratory values, and contraindications to ticagrelor or morphine.[9]

The trial was randomized, and although the pharmacists preparing the controls and treatments were unblinded, the physcians administering them were blinded. Those who analyzed the pharmacokinetics and pharmacodynamics were also blinded. After an overnight fast by the patients, physicians gave them a LD of 180 mg ticagrelor. The VASP assay and multiple electrode aggregometry were used to measure the ticagrelor effects. The researchers assessed pharmacokinetics using liquid chromatography tandem mass spectrometry. Pharmacokinetic calculations were made using Kinetica 2000 version 3.0. Before the crossover trial began, the trial allowed for a fourteen-day washout period.[9]

In summary, the 24 healthy volunteers were co-administered 180 mg ticagrelor with either placebo or the recommended 5 mg of morphine.[1,9] The researchers looked at the pharmacokinetics of ticagrelor and its antiplatelet effects. The results state a delay in

ticagrelor absorption when administered with morphine ($P<0.05$) by 1 hour and a reduced level of its active metabolite by 25-31% ($P\leq0.03$). Hobl et al state that morphine reduced the drug exposure (AUC) by 22-23% ($P\leq0.01$). The researchers found and explain that the pharmacodynamics of ticagrelor on platelet aggregation in whole blood, platelet plug formation, and VASP phosphorylation are not affected by morphine. They concluded that morphine decreases the pharmacokinetic effects of ticagrelor but does not inhibit its pharmacodynamic effects.[9]

The researchers explain that in regards to the pharmacokinetic interactions of morphine and ticagrelor, there was a delay in maximum plasma concentrations of ticagrelor (T_{max}:180 vs 120 mins, P=0.016) and the active metabolite (240 vs 180 min, P=0.023). Hobl et al state that morphine reduced both the C_{max} of ticagrelor (from 1222 to 913 ng/mL, p=0.015) and reduced the active metabolite (from 325 to 242 ng/mL, P=0.028) and the total exposure as measured by AUC_{0-n} by 22% and 23% for ticagrelor and it's active metabolite (ticagrelor: 228 110 vs 177 617 ng*h/mL, p=0.011, ticagrelor active metabolite: 67 200 vs 52 882 ng*h/mL, p=0.009). They say that morphine did not influence pharmacodynamics of ticagrelor, neither whole blood aggregation nor platelet plug formation under high shear rates. Ticagrelor prolonged collagen/ADP induced closure times (CADP-CT) 6 hours after intake from a median of 96 to 167 seconds under placebo and from 94 to 165 seconds when morphine was co-administered (for both periods: $P<0.001$).[9]

The researchers closed their study with the discussion point that ticagrelor has the potential to overcome the pharmacodynamic problems of the clopidogrel-morphine interaction. Morphine slows gastric emptying[9,24] and morphine did indeed delay drug

absorption, leading to a lower concentration of ticagrelor and its active metabolite by 20-30%. However, the US Food and Drug Administration classifies a drug-to-drug interaction as a difference of less than or equal to 25% in AUC.[9,28] Hobl et al state the maximal inhibition of platelets after 60-75 minutes in both treatment periods with and without morphine shows a lack of morphine on ticagrelor pharmacodynamics.[9]

Researchers state that providers can be confident that a LD of 180 mg ticagrelor is potent enough to at least partially overcome the previously observed drug-to-drug interaction of clopidogrel and morphine, so ticagrelor can potentially be an effective alternative to clopidogrel when morphine is being co-administered.[9] However, the study reassures previous studies[7,9,15] noting that reduced blood flow in sick and hemodynamically unstable patients may compromise drug absorption or decrease peak levels of active metabolite. Morphine has an effect on drug absorption already may be more potent on these individuals along with the utilized antiplatelets. Overall, Hobl et al affirm that morphine moderately decreases ticagrelor plasma concentrations but does not inhibit its antiplatelet effects in healthy volunteers.[9] See Table II for summary of findings.

The researchers point out several lmitations of this study: one limitation is the timing of the morphine administration, which was given at a predefined point, which is not equivalent to an emergency situation. The dosing of the ticagrelor was administered with exactly 250 mL of tap water, which differs from an emergent situation. They state their trial was not designed to observe the pharmacodynamics for 24 hours and that it cannot rule out other possible drug-drug interactions that would likely happen in the emergency room with various patients. In this study they only looked at patients on morphine and ticagrelor without influence of any other drug. Another limitation is that

the study was performed on healthy patients rather than STEMI patients, whose absorption may be compromised through reduced splanchnic blood flow.[9]

Hobl et al Study on Morphine Interactions with Prasugrel

This randomized, double-blind, placebo-controlled, cross-over trial[17] looked to study the potential drug-to-drug interactions between prasugrel and morphine. The researchers state they chose to look at prasugrel because it is a more potent $P2Y_{12}$ inhibitor in comparison with clopidogrel which was studied prior this study.[8] Where clopidogrel is converted into its active metabolite in two steps, they state prasugrel is hydrolyzed by esterase to an immediate metabolite and requires only one further CYP-dependent oxidation step to generate its active compound.[17] Thus, they explain, prasugrel poses less variability in response between patients and higher efficacy. The researchers suspected that the drug interaction between morphine and prasugrel would be minor as that compared to clopidogrel.[17]

The study used 12 healthy volunteers with the inclusion criteria being: greater than or equal to 18 years of age, non-pregnant, and the ability to comprehend the full nature and purpose of the study. The exclusion criteria were: intake of NSAIDS or other platelet inhibitors, known coagulation disorders, renal or liver disease, chronic infectious diseases, clinically relevant abnormal laboratory values, and contraindications to prasugrel or morphine.[17]

The trial was randomized, and although the pharmacists preparing the controls and treatments were unblinded, the physcians administering them were blinded. Those who analyzed the pharmacokinetics and pharmacodynamics were also blinded. After an

overnight fast by the patients, physicians gave them a LD of 60 mg prasugrel. The VASP assay and multiple electrode aggregometry were used to measure the prasugrel effects. The researchers assessed pharmacokinetics using liquid chromatography tandem mass spectrometry. Pharmacokinetic calculations were made using Kinetica 2000 version 3.0. Before the crossover trial began, the trial allowed for a fourteen-day washout period.[17]

In summary, 12 healthy volunteers were co-administered 60 mg prasugrel with either placebo or the recommended 5-mg morphine.[1,9] The researchers looked at the pharmacokinetics of prasugrel as well as its antiplatelet effects. The researchers state the results show that morphine neither diminished total drug exposure (AUC), which was the primary endpoint, nor significantly delayed drug absorption of prasugrel. However, they explain, morphine did reduce maximal plasma concentrations (C_{max}) of prasugrel metabolite by 31% (P=0.019). Hobl et al state morphine slightly delayed the onset of maximal inhibition of platelet plug formation under high shear rates (30 vs 20 minutes), but this was found to not be significant. Whole blood aggregation was not influenced in this study. The researchers concluded that morphine significantly decreases the maximal plasma concentrations of prasugrel and its active metabolite, but they make clear it does not diminish the effects of prasugrel on platelets to a clinically relevant degree in healthy volunteers. Overall, Hobl et al state that the decrease in C_{max} of prasugrel and its active metabolite caused by morphine co-administration should gain relevance in STEMI patients.[17]

The researchers stated that in regards to the pharmacokinetic interactions of morphine and prasugrel, morphine did not significantly reduce total exposure as measured by $AUC_{0\text{-}n}$ (69 573 vs 65 991 ng x h/mL, P=0.239), which was the primary

endpoint. The time of maximal plasma concentrations of prasugrel active metabolite (30 vs 38 min, P=0.798) was not influenced by morphine. Hobl et al state that morphine however, did reduce the C_{max} of prasugrel and its active metabolite by 31% from 1388 to 951 ng/mL (P=0.019). Whole blood aggregation of prasugrel was not influenced by the morphine however, it caused a slight insignificant delay in the maximal inhibition of the platelet plug formation under high shear rates. Hobl et al state that overall, morphine did not reduce the total drug exposure as measured by the AUC_{0-n}, which was the primary endpoint. Morphine also did not slow the T_{max} of prasugrel active metabolite. The researchers state that morphine did reduce the maximal plasma concentration of prasugrel active metabolite by 31%, which would prove significant if morphine had effects on the pharmacodynamics of prasugrel.[17]

The researchers closed their study with the discussion point that the 60 mg LD of prasugrel appears to be adequate to inhibit platelet function in healthy volunteers. They state that morphine co-administration moderately decreases the maximal plasma concentration of prasugrel and its active metabolite, but it does not inhibit its effects on platelets to a clinically relevant degree in healthy volunteers. See Table II for summary of findings.

The researchers discuss limitations of their study. One limitation is that the study was performed on healthy patients rather than STEMI patients, whose absorption may be compromised through reduced splanchnic blood flow.[17,27] Another limitation of the study is the very small sample size. Twelve patients total may not be enough to draw strict conclusions in the generalized population.

DISCUSSION

The purpose of this systematic review of the literature was to explore the effects of morphine in the various recommended antiplatelets in ACS. The studies[7-9,17] used in this review examined morphine, the recommended treatment for pain in patients presenting with ACS, and explored its effects on the pharmacodynamics and pharmacokinetics on the three most highly used antiplatelets in the setting if ACS, hypothesizing that morphine potentially inhibits antiplatelet efficacy. While morphine is the most widely recommended analgesic for treatment of chest pain in ACS, there has not been extensive research using randomized controlled trials on morphine or its effects on the other medicines used in treatment of ACS.[7-9,17] Morphine has even been associated with poor outcomes when used in patients for treatment of ACS.[7-10,17] If morphine is associated with less efficacious antiplatelet function in the setting of MI, perhaps clinicians need to look to other options for pain control in this patient population.

In the Hobl et al study on morphine and clopidogrel,[8] it was found that morphine delayed clopidogrel absorption, decreased plasma levels of the active metabolite of clopidogrel, and slowed and lowered its effects in healthy volunteers. The Hobl et al study on morphine effects on prasugrel[17] found that morphine decreased the maximal plasma concentrations of prasugrel, but did not diminish its effects in healthy volunteers. The Hobl et al study on morphine effects on ticagrelor[9] found that morphine moderately decreased plasma concentrations but did not inhibit its pharmacodynamics in healthy volunteers. The Parodi et. al study[7] found that morphine is associated with a delayed onset of action of both ticagrelor and prasugrel. Parodi et al stated that morphine maintained relatively higher $P2Y_{12}$ reactivity units and was associated with HRPR up to 4

hours after administration. Clopidogrel appears known now to have adverse effects when co-administered with morphine and its use is in question when ACS patients are being treated with morphine.[8,25] It appears that with the more potent ticagrelor and prasugrel,[7,9,15,17,22,23,25] the pharmacodynamics of these drugs may be able to overcome morphine's effects. The pharmacokinetics of these two antiplatelets however, continue to be affected by morphine.[7,9,17]

In looking at each study considered for the purposed of this systematic review, variability across the studies must be considered. The Hobl et. al studies[8,9,17] were RCTs and performed in a very controlled environment with precise timing and administration of each drug in question. In the Parodi et al study,[7] the researchers took patients across several emergency, real life events, thus the timing of the administration of morphine and antiplatelets was not as precisely measured as the Hobl et. al studies. Additionally, In the Parodi et. al study,[7] the administration of antiplatelets along with morphine was still within the realm of recommendations for the emergency room patient population,[1,7,29] but there likely was more variability in the timing of when the patients received the morphine and antiplatelets. In the Hobl et al studies,[8,9,17] the patients received a placebo of 0.9% NaCl whereas in the Parodi et al study,[7] instead of receiving a placebo, these patients did not receive morphine at all. Overall and regardless of the variability, similar pharmacodynamic and pharmacokinetic effects were seen.[7-9,17]

There were strong limitations in all three of the Hobl et al studies.[8,9,17] These studies each used a small sample size – between 12 and 24 patients. In addition to the small sample size, the Hobl et al studies[8,9,17] only used healthy volunteers to study the

effects of morphine in various antiplatelets. This can confuse results in that those in a real-life scenario being treated with morphine and antiplatelets are not necessarily considered healthy. Each Hobl et al study[8,9,17] addresses this large limitation. The important factor with this issue is that patients in an emergent setting can have varying degrees of hemodynamic stability, which can significantly affect the absorption and interactions of drugs.[17,27]

Early reperfusion is the goal in STEMI[1,7,29] and if a drug-to-drug interaction decreases the chances or speed of this occurring, this becomes a critical issue for patients. If the antiplatelet effects are diminished in patients with STEMI, treatment failure can be the end result.[8] Parodi et al[7] hypothesized that patients treated with morphine in these situations are at higher risk. Even though Hobl et al[9,17] found that prasugrel and ticagrelor in healthy patients do not have diminished pharmacokinetic effects when co-administered with morphine, Parodi et al[7] states it cannot be ruled out that patients who are acutely sick have hemodynamic disarrangement, adrenergic activation, and systemic vasoconstriction all compounding the effects that morphine already has.[7] Thus, it may be important and prudent for clinicians to think either about the dose of and specific antiplatelet they are using in patients with STEMI, but they must also think about the possibility of using alternate pain control methods.[14]

Future research in pain control in ACS will be very helpful. There is existing research on the hemodynamics of ill patients,[7-9,17,27,29] but research on specific analgesics and their effects on antiplatelets may provide some alternative ways to treat chest pain without a decrease in effect of these drugs. Hobl et al[8,9,17] postulated an RCT to clarify

the benefit-risk ratio of morphine in the setting of MI with severe chest pain. With early reperfusion as the main goal of STEMI,[1,7-9,17,30] a look into reperfusion techniques will provide help in treating patients more efficiently as myocardial ischemic relief is the best chest pain control strategy.[7] Kubica et al[31,32] is currently performing an ongoing RCT called the IMPRESSION trial. This trial is looking particularly at ticagrelor co-administration with morphine in patients presenting with myocardial infarction which will provide more insight into the drug to drug interactions of morphine and ticagrelor on acutely ill patients that the Hobl et al study[9] lacks.

CONCLUSION

Morphine administered for pain to patients presenting with ACS is associated with pharmacodynamic and pharmacokinetic effects of the antiplatelets clopidogrel, prasugrel, and ticagrelor. Morphine is shown to have significant drug-to-drug interactions with antiplatelets used in ACS but the effects appear different depending on the specific antiplatelet. The effects of morphine on Clopidogrel are the most profound, raising the question of whether Clopidogrel should even be used in STEMI patients. In conclusion, morphine decreases plasma concentrations of antiplatelets in both healthy patients and those in ACS. As emerging evidence continues to circulate on the drug-drug effects of morphine and antiplatelets, clinicians will do well to be aware of these effects as they choose specific agents for their patients in trying to provide the least harm and the most efficient reperfusion of ischemic vessels in myocardial infarction.

References

1. O'Gara PT. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (vol 127, pg e362, 2013). *Circulation*. 2013;128:E481-E481.
2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:485-510.
3. Fox KAA, Steg PG, Eagle KA, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA-J Am Med Assoc*. 2007;297:1892-1900.
4. Appleby P, Baigent C, Collins R, et al. Indications for Fibrinolytic Therapy in Suspected Acute Myocardial-Infarction - Collaborative Overview of Early Mortality and Major Morbidity Results from all Randomized Trials of More than 1000 Patients. *Lancet*. 1994;343:311-322.
5. Schomig A, Mehilli J, Antoniucci D, et al. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset - A randomized controlled trial. *JAMA-J Am Med Assoc*. 2005;293:2865-2872.
6. Gierlotka M, Gasior M, Wilczek K, et al. Reperfusion by Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial

Infarction Within 12 to 24 Hours of the Onset of Symptoms (from a Prospective National Observational Study [PL-ACS]). *Am J Cardiol*. 2011;107:501-508.

7. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation: Cardiovascular Interventions*. 2015;8.
8. Hobl E, Stimpfl T, Ebner J, et al. Morphine Decreases Clopidogrel Concentrations and Effects A Randomized, Double-Blind, Placebo-Controlled Trial. *J Am Coll Cardiol*. 2014;63:630-635.
9. Hobl E, Reiter B, Schoergenhofer C, et al. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. *Eur J Clin Invest*. 2016;46:7-14.
10. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: Results from the CRUSADE Quality Improvement Initiative. *Am Heart J*. 2005;149:1043-1049.
11. DeWaha S, Eitel I, Desch S, et al. Intravenous Morphine Administration and Reperfusion Success in ST-Elevation Myocardial Infarcttion: Insights from Cardiac Resonacne Imaging. *Clin Res Cardiol* (2015) 104:727–734
12. Farag M, Srinivasan M, Gorog D. Morphine use Impairs Thrombotic Status in Patients with St-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *J Am Coll Cardiol*. 2016;67:40-40 1p.
13. Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction. *N Engl J Med*. 2014;371:1016-1027.

14. Atar D, Agewall S. Morphine in myocardial infarction: balancing on the tight rope. *Eur Heart J*. 2016;37:253-255.
15. Parodi G, Valenti R, Bellandi B, et al. Comparison of Prasugrel and Ticagrelor Loading Doses in ST-Segment Elevation Myocardial Infarction Patients RAPID (Rapid Activity of Platelet Inhibitor Drugs) Primary PCI Study. *J Am Coll Cardiol*. 2013;61:1601-1606.
16. GRADE working group. GRADE website. http://gradeworkinggroup.org/. Accessed March 28, 2016.
17. Hobl E, Reiter B, Schoergenhofer C, et al. Morphine interaction with prasugrel: a double-blind, cross-over trial in healthy volunteers. *Clin res cardiol*. 2016;105:349-355.
18. Parodi G, Bellandi B, Valenti R, et al. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: The Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. *Am Heart J*. 2014;167:909-914.
19. Alexopoulos D, Gkizas V, Patsilinakos S, et al. Double Versus Standard Loading Dose of Ticagrelor Onset of Antiplatelet Action in Patients With STEMI Undergoing Primary PCI. *J Am Coll Cardiol*. 2013;62:940-941.
20. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized Assessment of Ticagrelor Versus Prasugrel Antiplatelet Effects in Patients with ST-Segment-Elevation Myocardial Infarction. *Circ -Cardiovasc Interv*. 2012;5:797-804.

21. Michelson AD, Frelinger,Andrew L.,,III, Braunwald E, et al. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. *Eur Heart J*. 2009;30:1753-1763.
22. Storey RF, Angiolillo DJ, Patil SB. Inhibitory Effects of Ticagrelor Compared With Clopidogrel on Platelet Function in Patients With Acute Coronary Syndromes The PLATO (PLATelet inhibition and patient Outcomes) PLATELET Substudy (vol 56, pg 1456, 2010). *J Am Coll Cardiol*. 2010;56:1895-1895.
23. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2009;361:1045-1057.
24. Nimmo WS, Heading RC, Wilson J, Tothill P, Prescott LF. Inhibition of gastric emptying and drug absorption by narcotic analgesics. *Br J Clin Pharmacol*. 1975;2:509-13.
25. Bates ER, Lau WC, Angiolillo DJ. Clopidogrel-Drug Interactions. *J Am Coll Cardiol*. 2011;57:1251-1263.
26. Siller-Matula JM, Huber K, Christ G, et al. Impact of clopidogrel loading dose on clinical outcome in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Heart*. 2011;97:98-105.
27. Bochner F, Lloyd J. Aspirin for Myocardial-Infarction - Clinical Pharmacokinetic Considerations. *Clin Pharmacokinet*. 1995;28:433-438.
28. Huang S-, Temple R, Throckmorton DC, Lesko LJ. Drug interaction studies: Study design, data analysis, and implications for dosing and labeling. *Clinical Pharmacology & Therapeutics*. 2007;81:298-304. 29 from D

29. Xanthopoulou I, Davlouros P, Tsigkas G, et al. Factors Affecting Platelet Reactivity 2 Hours After P2Y(12) Receptor Antagonist Loading in Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction - Impact of Pain-to-Loading Time. *Circulation Journal*. 2016;80:442-449.
30. Roffi M, Patrono C, Collet J, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267-+.
31. Kubica J, Adamski P, Ostrowska M, et al. Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction (IMPRESSION): study protocol for a randomized controlled trial. *Trials*. 2015;16:198
32. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J*. 2016;37:245-252.